REMARKS/ARGUMENTS

Claims 11, 22-25, and 40-43 are pending.

Claims 1-10, 12-21, and 26-39 have been cancelled.

Claims 11, 22-25, and 40-43 are rejected under 35 U.S.C. 103(a) over Halazy et al., EP1193268, Bennett et al., Cur. Opinion Pharmacol., 3(4):420-425 (2003), and Weber et al., US 3,454,635. The rejection is traversed because (a) Halazy et al. do not describe or suggest, explicitly or inherently, by itself or combined with Bennett et al. and Weber et al., the treatment of type II diabetes with the claimed sulfonamide compounds, (b) there is insufficient nexus between (i) autoimmune diseases and neuronal system disorders, and (ii) type II diabetes, and (c) one would not have reasonably expected that the Halazy et al. compounds would have treated a type II diabetes.

The claimed method is directed to treating type II diabetes with the claimed sulfonamide compounds.

(a) Halazy et al. do not describe or suggest, explicitly or inherently, by itself or combined with Bennett et al. Weber et al., the treatment of type II diabetes with the claimed sulfonamide compounds.
(b) Bennett et al. teach away from the claimed method

Halazy et al. disclose that the JNK signaling pathway is implicated in cell proliferation and could play an important role in autoimmune diseases (see, [001]-[0015]; [0056]-[0059]). Halazy et al. show that the disclosed generic compounds modulate the JNK pathway as JNK inhibitors, notably JNK2 and JNK3, and are useful for the treatment of the immune and neuronal system disorders (see, [0056]-[0059] and [0135]-[0137].

The Examiner points to the disclosure of Bennett et al. describing that the JNK pathway has a connection to insulin resistance in type II diabetes.

Although Bennett et al. disclose that one JNK inhibitor (CC105 small molecule different from the Halazy et al. compounds) has potential in treating insulin resistance and

obesity, it does not mean that all Halazy et al. compounds of general formula I are necessarily effective for treating type II diabetes.

Bozyczko-Coyne et al., *Curr. Drug Target – CNS & Neurol. Disorders*, 1:31-49, 42-43 (2002) (previously submitted) show that the JNK pathway is very complex, involves many levels of regulations, genes, proteins, and disorders. The JNK pathway is implicated in a large number of physiological and pathological functions. *See*, Bozyczko-Coyne et al., at 43-43. Moreover, the complexity of the organization and regulation at all levels within the JNK signaling cascade continues to evolve. Further, because of the complex cross talk within this signaling cascade as well as its cell type and response specific modulation, it is difficult to predict potential adverse events that might arise from pathway inhibition (Bozyczko-Coyne et al., page 43). Owing to the breadth of physiological functions mediated via signaling through the JNK family, direct inhibition at the level of the JNK could prove to have liabilities (Bozyczko-Coyne et al., page 31. right col.).

Thus, if one specific JNK inhibitor (CC105 small molecule different from the Halazy et al. compounds) of Bennett et al. has potential in treating insulin resistance, it does not mean that Halazy et al.'s compounds (useful for the treatment of the immune and neuronal system disorders) are effective for treating a type II diabetes because (1) the JNK pathway is very complex, and (2) there is insufficient nexus between (i) autoimmune diseases and neuronal system disorders and (ii) type II diabetes (see, below).

The Examiner is of the opinion that because (i) Halazy et al. describe the same compounds (page 36, lines 25-30) and that the compounds are effective modulator of the JNK pathway (page 2-3 and 9), and (ii) Bennett et al. suggest a connection of the JNK pathway with insulin resistance and type II diabetes, Halazy et al. and Bennett et al. make claims 11, 22, 25, 40, and 43 obvious.

Applicants submit that even when one specific JNK inhibitor (the CC105 small molecule different from the Halazy et al. compounds) of Bennett et al. has potential in treating insulin resistance, it does not mean that Halazy et al.'s compounds (useful for the treatment of the immune and neuronal system disorders and different from the CC105 small molecule) are also effective for treating a type II diabetes because (1) the JNK pathway is very complex, and (2) there is insufficient nexus between (i) autoimmune diseases and neuronal system disorders and (ii) type II diabetes; and (3) chemical arts are unpredictable.

In a recent decision, the Court stated that "[t]o the extend an art is unpredictable, as the chemical arts often are, *KSR*'s focus on these "identified, predictable solutions" may present a difficult hurdle because potential solutions are less likely to be genuinely predictable." *Eisai Co, Ltd. v. Dr. Reddy's Lab.*, 87 USPQ2d 1452, 1457, 533 F.3d. 1353 (Fed. Cir., 2008).

The claimed method provides treating type II diabetes with the claimed compounds of formula (I), which is characterized by an elevated level of insulin in the blood flow (see disclosure on page 1, lines 19-21). This hyperinsulinemia has been associated with obesity and PCOS, as mentioned in the specification on page 2, lines 7-15. The claimed compounds decrease the level of insulin in the blood flow, as disclosed on page 61, lines 3-6 of the specification, providing a specific mean of treating type II diabetes, obesity and PCOS.

Although Bennett et al. describe that in general, the JNK pathway is a novel target for the treatment of diabetes, this statement relies on the action of the JNK inhibitor CC105 which increases the insulin level, contrary to the compounds of the present invention (see Bennett et al., page 422, first column).

Therefore, Bennett et al. **teach away** from the claimed method because the claimed compounds decrease the level of insulin in the blood flow, while the JNK inhibitor CC105 of Bennett et al. increases the insulin level.

(c) There is insufficient nexus between (i) autoimmune diseases and neuronal system disorders and (ii) type II diabetes.

Autoimmune diseases relate to a vast spectrum of disorders involving the thyroid, lupus, multiple sclerosis, rheumatoid arthritis and others (see, the listing submitted previously). Type-II diabetes is not known to be an autoimmune disease. Thus, when administering compound as taught by Halazy et al., one would not necessarily, each and every time, also treat Type-II diabetes as claimed.

Halazy et al. is equivalent to the application referenced on page 2, last paragraph, WO 02/26733. The present specification discloses that WO 02/26733 describes using sulfonamide derivatives for treating neuronal disorders, autoimmune diseases, cancer and cardiovascular diseases.

In contrast, this specification describes using the claimed specific compounds in *in vivo* assay in db/db mice to determine anti-diabetic effect of the test compounds in a model of postprandial glycemia (page 60-61). The experiment on pages 60-61 shows that the blood glucose level and blood insulin were decreased in the treated animals compared to the untreated animals.

(d) One would not have reasonably expected that the Halazy et al.compounds would have treated a type II diabetes.

Bennett et al. at best suggest trying the JNK inhibitors for treatment type II diabetes (one of many disorders modulated via the JNK pathway), but do not support the conclusion that the Halazy et al. compounds treat a type II diabetes.

One would not have reasonably expected that the Halazy et al. compounds would have treated a type II diabetes because (a) the chemical art is unpredictable, (b) the JNK pathway is very complex; (c) Halazy et al. do not enable for treating all disorders related to the JNK pathway; (d) the Bennett et al. specific JNK inhibitor is different from the Halazy et

al. compounds, and (e) JNK1 and JNK2/JNK3 are not equally involved in the insulin resistance.

The Bennett et al. specific JNK inhibitor that has potential in treating insulin resistance is different from the Halazy et al. compounds and, therefore, it is unpredictable whether a diriment compound would have been effective for treating insulin resistance because the chemical art is unpredictable and the JNK pathway is very complex and involves many different genes and proteins.

Also, JNK1 and JNK2/JNK3 are not equally involved in the insulin resistance. Specifically, Halazy et al. disclose on page 30 data relating to JNK2 and JNK3. No data relating to JNK1 are provided. Halazy et al. also describe in the abstract that compounds of his invention are particularly efficient and selective inhibitors of JNK2 and 3. Although JNK1 is mentioned in the description, there is no indication that the compounds of Halazy et al. would be effective in the inhibition of JNK1 and JNK2/3.

Bennett et al. teach that JNK1 and JNK2 are not equally involved in the insulin resistance and JNK1 would be the privileged isoform involved in the insulin resistance (see page 421, bottom of second column). Therefore, the teaching of Bennett et al. does not provide support for using the JNK2/3 inhibitors disclosed in Halazy et al. Based on the teaching of Halazy et al., in view of Bennett et al., one skilled in the art would not have reasonably expected a success in treating diabetes II by using the compounds of Halazy et al.

Moreover, the publication of J. Hirosumi (Nature, 2002, pages 333-336; submitted previously) teaches that JNK1 but not JNK2 is involved in the progression of diabetes II (see, page 335 second column, 1st paragraph). This disclosure clearly teaches one skill in the art away from using the selective JNK2/3 inhibitors (selected in Halazy et al. for treating immune and neuronal system disorders) in treating a type II diabetes.

There would not have been a reasonable expectation of success that the Halazy et al. compounds would have treated a type II diabetes.

Thus, one would not have reasonably expected that the Halazy et al. compounds would have treated a type II diabetes because (a) the chemical art is unpredictable, (b) the JNK pathway is very complex; (c) Halazy et al. do not enable for treating all disorders related to the JNK pathway; (d) the Bennett et al. specific JNK inhibitor is different from the Halazy et al. compounds, and (e) JNK1 and JNK2/JNK3 are not equally involved in the insulin resistance.

The Examiner has alleged that combining two drugs well-known to treat a type II diabetes would have been obvious and would have produced an additive effect because Weber et al. describe benzenesulflonyl-urea as known anti-diabetic agents.

Weber et al. provide compounds structurally distinct from those of the present invention. Weber et al. do not provide a description or suggestion of using these compounds in combination with other anti-diabetic compounds, and, in particular, with the claimed compounds having specific properties discussed above.

Also, combining any two drugs that may treat the same disease does not necessarily provide an additive effect because of a possible drug interaction which may decrease the effect of each drug or provide a deleterious effect. One would not have reasonably expected an additive effect upon a combination of any two drugs for the same indication without actually conducting experiments.

For these reasons, claims 11, 22-24, and 40-43 are not obvious.

Applicants request that the rejection be withdrawn.

A Notice of Allowance for all pending claims is requested.

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